

# PATENT SPECIFICATION

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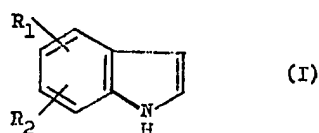
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(54) A PROCESS FOR THE MANUFACTURE OF INDOLES, A  
 PROCESS FOR THE PREPARATION OF  
 ORTHO-NITRO- $\beta$ -AMINOSTYRENES USEFUL THEREIN  
 AND CERTAIN ORTHO-NITRO- $\beta$ -AMINOSTYRENES *PER SE*

(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESellschaft, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

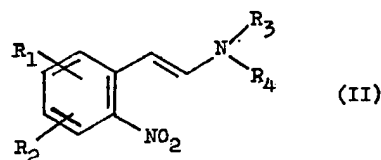
The present invention is concerned with a process for the manufacture of indoles. It is also concerned with a process for the preparation of *ortho*-nitro- $\beta$ -aminostyrenes useful in said process and with certain of said *ortho*-nitro- $\beta$ -aminostyrenes *per se*.

The indoles obtained according to the present invention have the general formula



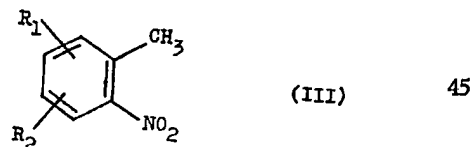
wherein  $R_1$  and  $R_2$  independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxycarbonyl, carbamoyl, halogen, amino, mono-lower alkyl-amino, di-lower alkylamino, lower alkoxy-carbonylamino, aryl-lower alkoxycarbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino, or di-lower alkoxymethyl or  $R_1$  and  $R_2$  together represent lower alkylendioxy.

According to one embodiment of this invention, the indoles of formula I hereinbefore are manufactured by treating an *ortho*-nitro- $\beta$ -aminostyrene of the general formula



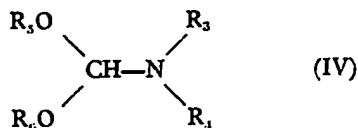
wherein  $R_1$  and  $R_2$  have the significance given earlier and  $R_3$  and  $R_4$  independently represent lower alkyl or  $R_3$  and  $R_4$  together represent lower alkylene, with a reducing agent.

According to another embodiment of this invention, the *ortho*-nitro- $\beta$ -aminostyrenes of formula II hereinbefore are prepared by condensing an *ortho*-nitrotoluene of the general formula



wherein  $R_1$  and  $R_2$  have the significance given earlier,

with a formamide acetal of the general formula



wherein  $\text{R}_3$  and  $\text{R}_1$  have the significance given earlier and  $\text{R}_5$  and  $\text{R}_6$  independently represent lower alkyl, aralkyl or cycloalkyl or  $\text{R}_5$  and  $\text{R}_6$  together represent lower alkylene.

According to a further embodiment of this invention, the indoles of formula I hereinbefore are manufactured by a two-step process which comprises condensing an *ortho*-nitro-toluene of formula III with a formamide acetal of formula IV and treating the resulting *ortho*-nitro- $\beta$ -aminostyrene of formula II with a reducing agent.

According to a still further embodiment of this invention, there are provided certain novel *ortho*-nitro- $\beta$ -aminostyrenes of formula II, namely those in which at least one of  $\text{R}_5$  and  $\text{R}_6$  is other than methyl when one of  $\text{R}_1$  and  $\text{R}_2$  represents hydrogen and the other represents hydrogen or methyl in the 3-position.

In the case where  $\text{R}_1$  or  $\text{R}_2$  represents a di-lower alkoxy methyl group in the formulae given above, it is preferably a dimethoxy-methyl group.

As used in this description and in the accompanying claims, the term "lower alkyl", when taken alone or in combination, denotes a straight-chain or branched-chain saturated hydrocarbon group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*butyl, neopentyl, pentyl and heptyl. The term "lower alkoxy", when taken alone or in combination, denotes a lower alkyl ether group in which the lower alkyl group is as defined earlier, for example, methoxy, ethoxy, propoxy and pentoxy. The term "halogen" denotes the four halogens, bromine, chlorine, fluorine and iodine. The term "aryl" denotes phenyl or phenyl bearing one or more halogen, trifluoromethyl, lower alkyl, lower alkoxy, nitro, amino, lower alkyl-amino and/or di-lower alkylamino substituents. The term "aryloxy" denotes an aryl ether group in which the aryl group is as defined earlier, for example, phenoxy. The term "acyl" denotes an alkanoyl group derived from an aliphatic carboxylic acid containing from 1 to 7 carbon atoms, for example, formyl, acetyl and propionyl or an aroyl group derived from an aromatic carboxylic acid such as benzoyl. The term "acyloxy" denotes an alkanoyloxy group derived from an aliphatic carboxylic acid containing from 1 to 7 carbon atoms, for example, formyloxy, acetoxy and propionyloxy or an aroyloxy group de-

rived from an aromatic carboxylic acid such as benzoyloxy. The term "lower alkylene dioxy" denotes an alkylene diether group containing from 1 to 7 carbon atoms such as methylenedioxy, ethylenedioxy and propylenedioxy. The term "lower alkylene" denotes a hydrocarbon group containing 2 to 5 (preferably 2 or 3) carbon atoms such as ethylene, propylene, butylene and pentylen. The term "aralkyl" denotes a lower alkyl group in which one or more of the hydrogen atoms have been replaced by an aryl group (e.g. benzyl). The term "cycloalkyl" denotes a cyclic hydrocarbon group containing from 3 to 6 carbon atoms.

Examples of aryl-lower alkoxy groups are benzyloxy, 1-phenylethoxy and 2-chlorobenzyloxy. Examples of aryl-hydroxymethyl groups are phenylhydroxymethyl and *p*-chlorophenylhydroxymethyl. Examples of lower alkoxy-carbonyl groups are methoxycarbonyl and ethoxycarbonyl. Examples of mono-lower alkylamino groups are methylamino, ethylamino, propylamino, isopropylamino, butylamino and pentylamino. Examples of di-lower alkylamino groups are dimethylamino, diethylamino, ethylmethylamino and dipropylamino. Examples of lower alkoxy-carbonylamino groups are methoxycarbonylamino and ethoxycarbonylamino. Examples of aryl-lower alkoxy-carbonylamino groups are benzyloxy-carbonylamino and *p*-chlorobenzyloxy-carbonylamino. Examples of acylamino groups are formylamino, acetylamino, propionylamino and benzoylamino. Examples of N-lower alkylacylamino groups are N-methylacetylamin, N-methylformylamin and N-ethylacetylamin. Examples of di-lower alkylformamidino groups are dimethylformamidino and diethylformamidino.

It will be appreciated that the *ortho*-nitro- $\beta$ -aminostyrenes of formula II have the *trans* configuration.

In a preferred aspect of the present invention,  $\text{R}_1$  and  $\text{R}_2$  independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, acyloxy, formyl, aroyl, halogen, amino or acylamino or  $\text{R}_1$  and  $\text{R}_2$  together represent lower alkylendioxy and  $\text{R}_5$ ,  $\text{R}_6$  and  $\text{R}_3$  independently represent lower alkyl or  $\text{R}_5$  and  $\text{R}_1$  or  $\text{R}_6$  and  $\text{R}_1$  together represent lower alkylene.

In a most preferred aspect of the invention, *o*-nitro-toluene is condensed with N,N-dimethylformamide dimethyl acetal to yield  $\beta$ -dimethylamino-2-nitrostyrene which is hydrogenated to yield indole.

As will be evident from the foregoing, the present invention provides a novel route to indoles. It provides a novel and significant route to many indoles of commercial value and is particularly salient in providing such indoles with greater efficiency than heretofore known in prior processes.

Broadly stated, the process of the present

invention involves condensing the methyl function of an *ortho*-nitro-toluene with the formyl radical of a formamide acetal to yield a nitrobenzene derivative which bears a N,N-disubstituted aminovinyl function in the *ortho*-position to the nitro group and thereafter reducing the nitro group to an amino group with concurrent displacement of the N,N-disubstituted amino function and cyclization to form an indole nucleus.

The *ortho*-nitrotoluenes of formula III are known or can be prepared by known procedures. Examples of such *ortho*-nitrotoluenes are 3 - methyl - 4 - nitrobiphenyl, 2 - methyl - 3 - nitrobenzyl alcohol, 3 - nitro- *p* - toluamide, 4 - methyl - 3 - nitrobenzophenone, 3 - nitro- *p* - toluic acid methyl ester, N,N - dimethyl - 3 - nitro - *p* - toluidine, 3 - nitro - *p* - toluic acid, 4 - methyl - 3 - nitrobenzophenone, N - methyl - 3 - nitro - *p* - toluidine and 3 - nitro - *p* - toluidine.

The formamide acetals of formula IV are known or can be prepared by known procedures. A preferred group of formamide acetals of formula IV comprises, for example, N,N - dimethylformamide diethyl acetal, N,N-dimethylformamide dimethyl acetal, N-formylpyrrolidine dimethyl acetal, 2-dimethylamino - 1,3 - dioxolane, N - formyl - piperidine dimethyl acetal, N,N-dimethylformamide dibenzyl acetal, N,N-dimethylformamide dicyclohexyl acetal, N,N-dimethylformamide diisopentyl acetal, N,N-dimethylformamide diisopropyl acetal and N,N-dimethylformamide di-*n*-heptyl acetal.

The condensation of an *ortho*-nitrotoluene of formula III with a formamide acetal of formula IV can be carried out in the presence or absence of an inert organic solvent. Preferably, the condensation is carried out in the presence of a polar aprotic solvent such as, for example, N,N-dimethylformamide (DMF), diethyleneglycol dimethyl ether (diglyme) and hexamethylphosphortriamide (HMPT). The conditions employed for the condensation are not narrowly critical. Thus, the condensation can be carried out at a temperature in the range of from room temperature to the reflux temperature of the condensation mixture. Preferably, the condensation is carried out at a temperature in the range of from 100°C to 160°C. Most conveniently, the condensation is carried out at the reflux temperature of the condensation mixture. The condensation may be carried out at atmospheric or super-atmospheric pressures. Conveniently, it is carried out at atmospheric pressure.

In a preferred aspect of this process, R<sub>1</sub> and R<sub>2</sub> each represents methyl, and one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen and the other represents hydrogen or methyl in the 3-position.

The *ortho*-nitro- $\beta$ -aminostyrenes of formula II are reduced chemically or catalytically to yield the corresponding indole deri-

vatives of formula I. The catalytic reduction may be carried out in any conventional manner, but it is preferably carried out at about room temperature with a hydrogen pressure of from 1 to 10 atmospheres. Any suitable hydrogenation catalyst may be employed. Examples of suitable hydrogenation catalysts are chromium, molybdenum, tungsten, platinum, palladium, rhodium, cobalt, nickel and ruthenium, their oxides, and combinations thereof such as, for instance, the oxides of cobalt or molybdenum in admixture and including cobalt molybdate. The preferred hydrogenation catalyst is palladium or RANEY nickel as well as other platinum group metals. Conveniently, the catalyst may be supported on carbon, for example charcoal.

Advantageously, the catalyst may be utilized in the presence of an inert solvent, for example, an alkanol such as methanol and ethanol, a hydrocarbon such as benzene, toluene, ethyl acetate and DMF. Most preferably, benzene is utilized.

The chemical reduction may be effected in a conventional manner; for example, with a metal such as iron, zinc or tin in an organic or inorganic acid such as acetic acid or hydrochloric acid, with stannous chloride in hydrochloric acid, with ferrous sulfate, with sodium dithionate, with sodium or ammonium sulfide or hydrosulfide. The conditions for the chemical reduction are not critical. Preferably, it is effected at a temperature in the range of from about room temperature to the reflux temperature of the mixture in the presence of a solvent such as water or a water miscible solvent, for example, an alkanol such as methanol, ethanol or tetrahydrofuran.

While, in general, the substituents represented by R<sub>1</sub> and R<sub>2</sub> are unaffected by the condensation and subsequent reduction, in certain cases they may be affected. For instance, during the condensation, a carboxyl group may be converted to an ester group and a phenolic hydroxyl group may be converted to a phenolic ether. Also, for instance, a dialkoxymethyl group can be retained or hydrolyzed. In the presence of acid, the dialkoxymethyl group is cleaved while, if no acid is present, it is retained.

Upon completion of the reduction, the end products, for example, indole, may be recovered utilizing conventional means such as crystallization, distillation or steam distillation. The indoles of formula I, are well documented in the literature and are useful for many purposes, for example, as intermediates in the preparation of amino acids, alkaloids and tryptamines. Thus, for example, indole, 6-methoxyindole and 5-benzyloxyindole can be utilized as intermediates in the preparation of tryptophan, reserpine and serotonin, respectively.

The following Examples illustrate the in-

vention. All temperatures are in degrees Centigrade.

#### EXAMPLE 1

A one liter three-necked flask fitted with a thermometer, a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet was charged with 137 g of *o*-nitrotoluene, 191 g of *N,N*-dimethylformamide diethyl acetal and 235 ml of *N,N*-dimethylformamide. The flask was immersed in a preheated oil bath which was maintained at 165° for 24 hours. The pot temperature was maintained at 145–150° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation under an atmosphere of nitrogen. The remaining dark red liquid was then transferred to a flask and distilled to yield 186 g (97 per cent) of *trans-β*-dimethylamino-2-nitrostyrene as a dark red liquid having a boiling point of 125°/0.03 mm.

Anal. Calcd. for  $C_{11}H_{12}N_2O_2$ :

C, 62.48; H, 6.29; N, 14.58

Found:

C, 62.66; H, 6.63; N, 14.50

#### EXAMPLE 2

In a one liter three-necked flask fitted with a thermometer, a vacuum-jacketed, silvered column with GOODLOE packing, distillation head and a receiver with a nitrogen inlet were placed 137.1 g of *o*-nitrotoluene, 121.6 g of 98% *N,N*-dimethylformamide dimethyl acetal and 200.0 g of *N,N*-dimethylformamide. The condensation mixture was heated at reflux for 24 hours. The temperature was maintained at 135–155° by continuous distillation of the methanol as it formed. A total of 56.0 g of distillate was collected.

By careful distillation, 206.3 g of *N,N*-dimethylformamide (b.p. 51–55°/20 mm) and 13.0 g (10%) of *o*-nitrotoluene (b.p. 109°/23 mm) were removed from the condensation mixture to give a residual dark liquid which, after distillation, yielded 167.0 g (87%) of *trans-β*-dimethylamino-2-nitrostyrene as a dark red liquid having a boiling point of 128°/0.05 mm.

#### EXAMPLE 3

A 50 ml glass-lined autoclave containing 15.6 g of 95% *N,N*-dimethylformamide diethyl acetal and 13.7 g of *o*-nitrotoluene was pressurized with nitrogen in an autoclave to 35 atmospheres and then heated to 155° for 24 hours.

The resulting red solution was distilled from a 50 ml CLAISEN flask. The forerun (b.p. up to 60°/0.2 mm) was discarded. The red liquid distilling at 134–136°/0.25 mm amounted to 13.4 g (70%) of *trans-β*-dimethylamino-2-nitrostyrene.

#### EXAMPLE 4

A solution containing 178.6 g of *trans-β*-dimethylamino-2-nitrostyrene in 2.5 liters of benzene containing 2.0 g of 10% palladium on carbon was shaken in a 4 liter autoclave under an initial hydrogen pressure of 4.55 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene solution was then extracted with three 600 ml portions of 1N sulfuric acid and two 500 ml portions of water. The aqueous phases were back-washed in a countercurrent manner with 500 ml of benzene. The combined benzene phases were dried over a mixture of anhydrous sodium sulfate and potassium carbonate, filtered and evaporated to give 96.0 g of a greyish solid which, on rapid distillation under nitrogen, gave 91.3 g of a slightly yellowish solid having a melting point of 51–53°. The distillate, on fractionation, gave a total of 87.4 g (80%) of indole as a white solid having a melting point of 52.5–53.5°.

#### EXAMPLE 5

A) The preparation of the starting material:

To a solution containing 15.3 g of 3-methyl-4-nitrophenol in 200 ml of absolute ethanol stirred under nitrogen, 5.40 g of sodium methoxide were added over a period of 15 minutes. The solution was then stirred at reflux for 1.5 hours. Thereafter, 12.66 g of benzyl chloride were added dropwise and the reaction was maintained at reflux for 20 hours. The ethanol was evaporated from the reaction mixture. To the residue were added 200 ml of ether and 100 ml of 1N sodium hydroxide. The ether solution was washed with an additional 100 ml of 1N sodium hydroxide solution and then with 100 ml of water. The aqueous phases were washed with three 300 ml portions of ether in a countercurrent manner. The combined aqueous phases were acidified with phosphoric acid and extracted with three 200 ml portions of methylene chloride. The combined methylene chloride layers were dried ( $Na_2SO_4$ ) and evaporated to dryness to give 2.8 g (18%) of recovered 3-methyl-4-nitrophenol. The ether extracts were dried ( $Na_2SO_4$ ) and evaporated to dryness. The aqueous phases were discarded and the organic phases dried ( $Na_2SO_4$ ) and evaporated to dryness. The product was crystallized from 75 ml of methanol yielding 15.1 g (62%) of 5-benzyloxy-2-nitrotoluene as white needles having a melting point of 70.5–71.5°.

Anal. Calcd. for  $C_{11}H_{13}NO_3$ :

C, 69.13; H, 5.39; N, 5.76

Found:

C, 69.34; H, 5.44; N, 5.69

## B) The condensation:

A 100 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet was charged with 24.32 g of 5-benzyloxy-2-nitrotoluene, 23.0 g of N,N-dimethylformamide diethyl acetal and 25 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath at 160° for 40 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol as it was formed.

The volatile components were removed under reduced pressure on a rotary evaporator. The red solid residue, crystallized from 300 ml of ether and 25 ml of benzene, yielded 23.3 g (78%) of *trans*-5-benzyloxy- $\beta$ -dimethylamino-2-nitrostyrene as red needles having a melting point of 97.5—99°.

Anal. Calcd. for  $C_{17}H_{18}N_2O_3$ :

C, 68.44; H, 6.08; N, 9.39

Found:

C, 68.73; H, 6.13; N, 9.46

## EXAMPLE 6

A solution containing 15.0 g of *trans*-5-benzyloxy- $\beta$ -dimethylamino-2-nitrostyrene in 250 ml of 80% ethanol (N,N-dimethylformamide) and 1 teaspoonful of RANEY nickel were shaken under a hydrogen atmosphere in a PARR apparatus until hydrogen absorption ceased. The catalyst was removed by filtration. The solvents were removed under a vacuum. The residue was sublimed and the sublimate was crystallized from ether/(petroleum ether) to yield 5.1 g (45%) of 5-benzyl-oxyindole as white needles having a melting point of 103—105°.

## EXAMPLE 7

A 100 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet was charged with 18.1 g of 3-methyl-4-nitrobenzoic acid, 37.6 g of N,N-dimethylformamide diethyl acetal and 25 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath at 100° for 4.5 hours. The pot temperature was maintained above 135° by continuous distillation of the ethanol formed during the condensation.

The volatile components were removed by vacuum distillation. After trituration with petroleum ether, the residue crystallized to give 18.5 g (70%) of *trans*-3-( $\beta$ -dimethylaminovinyl)-4-nitrobenzoic acid ethyl ester as a red solid having a melting point of 55—56.5°.

Anal. Calcd. for  $C_{17}H_{18}N_2O_4$ :

C, 59.08; H, 6.10; N, 10.60

Found:

C, 59.02; H, 6.00; N, 10.63

## EXAMPLE 8

A solution containing 7.5 g of *trans*-3-( $\beta$ -

dimethylaminovinyl)-4-nitrobenzoic acid ethyl ester in 250 ml of absolute ethanol and 715 mg of 10% palladium on carbon were shaken under 3.5 atmospheres of hydrogen in a PARR apparatus until hydrogen absorption ceased. The catalyst was removed by filtration and the filtrate was dried. The residue was applied to a column containing 100 g of magnesia/(silica gel). The fractions containing the product (eluted with benzene) were combined. Crystallization from ether/(petroleum ether) yielded 2.1 g (39%) of 5-indolecarboxylic acid ethyl ester as white crystals having a melting point of 95—96°.

Anal. Calcd. for  $C_{11}H_{11}NO_2$ :

C, 69.82; H, 5.86; N, 7.40

Found:

C, 70.14; H, 5.87; N, 7.45

## EXAMPLE 9

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 17.16 g of 2-chloro-6-nitrotoluene, 24 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 6 hours. The pot temperature was maintained at about 140° by continuous distillation of the ethanol formed during the condensation.

The volatile components were removed by vacuum distillation at 25°/3 mm and the product was distilled to give 20.2 g (89%) of *trans*-6-chloro- $\beta$ -dimethylamino-2-nitrostyrene as a dark red liquid having a boiling point of 111°/0.03 mm.

Anal. Calcd. for  $C_{10}H_{11}ClN_2O_2$ :

C, 52.99; H, 4.89; Cl, 15.67; N, 12.36

Found:

C, 53.18; H, 4.57; Cl, 15.75; N, 12.23

## EXAMPLE 10

To a solution containing 10.40 g of *trans*- $\beta$ -dimethylamino-6-chloro-2-nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY-nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with three 75 ml portions of 1M sulfuric acid and two 100 ml portions of water. The aqueous phases were back-washed with 125 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $K_2CO_3$ ), filtered, and evaporated to give 5.4 g of dark green oil which, on distillation, yielded 4.75 g of a yellow liquid having a boiling point of 116°/2 mm. After redistillation there were obtained 4.41 g (63%) of 4-chloroindole as a

slightly yellow liquid having a boiling point of 90°/0.04 mm.

#### EXAMPLE 11

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 34.3 g of 5-chloro-2-nitrotoluene, 55.0 g of 85% N,N-dimethylformamide diethyl acetal and 200 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 7 hours. The pot temperature was maintained above 146° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation (70° bath/0.5 mm). The resulting dark red residue was crystallized from 275 ml of ether/(petroleum ether) to give 33.2 g of red crystals having a melting point of 81.5—82.5°. From the mother liquor an additional 6.6 g of crystals having a melting point of 78—81° were obtained. Thus, the total yield of *trans*-5-chloro- $\beta$ -dimethylamino-2-nitrostyrene was 39.8 g (88%).

Anal. Calcd. for  $C_{11}H_{11}ClN_2O_2$ :

C, 52.99; H, 4.89; Cl, 15.64; N, 12.36

Found:

C, 52.65; H, 5.20; Cl, 15.69; N, 11.89

#### EXAMPLE 12

To a solution of 11.6 g of *trans*-5-chloro- $\beta$ -dimethylamino-2-nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen had ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1N sulfuric acid, two 100 ml portions of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 6.8 g of a greenish solid. Distillation yielded 6.26 g of an almost white solid which was dissolved in ether and percolated through about a gram of alumina. After removal of the ether, the residue was crystallized from 30 ml of petroleum ether to give 6.0 g (78%) of 5-chloroindole as white plates having a melting point of 71—72°.

#### EXAMPLE 13

In a 100 ml three-necked round-bottom flask fitted with a thermometer and a condenser with a nitrogen inlet were placed 17.15 g of 4-chloro-2-nitrotoluene and 18.00 g of N,N-dimethylformamide diethyl acetal. The flask was immersed in an oil bath at 145°

for 58 hours. After 24 hours an additional 3 g of acetal were added.

The volatile components were removed by vacuum distillation under nitrogen until the head temperature began to rise to 158°/0.09 mm. Subsequent distillation gave 12.0 g (57%) of *trans*-4-chloro- $\beta$ -dimethylamino-2-nitrostyrene as a red liquid having a boiling point of 158°/0.09 mm.

Anal. Calcd for  $C_{11}H_{11}ClN_2O_2$ :

C, 52.99; H, 4.89; Cl, 15.63; N, 12.36

Found:

C, 52.96; H, 4.89; Cl, 15.63; N, 12.30

#### EXAMPLE 14

A solution of 4.50 g of *trans*-4-chloro- $\beta$ -dimethylamino-2-nitrostyrene in 250 ml of absolute ethanol and 1 teaspoonful of RANEY nickel were shaken under a hydrogen atmosphere until hydrogen absorption ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was applied to a column containing 25 g of magnesia/(silica gel). The fractions containing the product (eluted with 5% benzene/hexane) were combined. Crystallization from benzene/hexane yielded 1.59 g (52%) of 6-chloroindole as white crystals having a melting point of 89—89.5°.

#### EXAMPLE 15

A 500 ml three-necked flask fitted with a thermometer and 15 cm VIGREUX column connected to a descending condenser with a receiver and nitrogen inlet was charged with 33.0 g of 5-nitropseudocumene, 48.3 g of N,N-dimethylformamide diethyl acetal and 200 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 165°, for 31 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The residue was triturated with methanol and the insoluble material crystallized from 600 ml of methanol to give 25.5 g (58%) of *trans*- $\beta$ -dimethylamino-2,5-dimethyl-4-nitrostyrene as dark red needles having a melting point of 130—131°.

Anal. Calcd. for  $C_{15}H_{17}N_2O_2$ :

C, 65.43; H, 7.32; N, 12.72

Found:

C, 65.17; H, 7.29; N, 12.88

The methanol triturate was evaporated and the residue digested with petroleum ether (20  $\times$  100 ml). The petroleum ether extracts yielded 14.5 g of a red solid ( $\beta$ -dimethylamino-4,5-dimethyl-2-nitrostyrene contaminated with a small amount of  $\beta$ -dimethylamino-2,5-dimethyl-4-nitrostyrene) which, after dissolution in 50 ml of ethanol, was added to a solution of 140 g of ferrous sulfate heptahydrate, 500 ml of water and

85 ml of concentrated ammonia. The resulting mixture was heated at reflux for 15 minutes and the precipitate which formed was removed by filtration. The filtrate was concentrated by evaporation and then extracted with three 200 ml portions of carbon tetrachloride. The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated. The residue was percolated through a dry column of alumina with 5% benzene/hexane. The fractions were combined and the solvents removed to give 450 mg of a white solid. The material was crystallized from 8 ml of petroleum ether to give 277 mg of 5,6-dimethylindole as white needles having a melting point of 64.5—65.5°.

#### EXAMPLE 16

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 20.00 g of 5-fluoro-2-nitrotoluene, 56.0 g of 85% N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 3.5 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm and the residual dark red solid was crystallized from 70 ml of ether/(petroleum ether) to give 20.55 g of red needles having a melting point of 52—55°. The mother liquor, after removal of the solvents and distillation, yielded an additional 4.24 g of red solid having a melting point of 56—58°. The total yield was 24.79 g (92%). A portion of the material was recrystallized to give *trans*- $\beta$ -dimethylamino - 5 - fluoro - 2 - nitrostyrene as red crystals having a melting point of 56—58°.

Anal. Calcd. for  $\text{C}_{11}\text{H}_{11}\text{FN}_2\text{O}_2$ :

C, 57.14; H, 5.28; F, 9.03; N, 13.32

Found:

C, 57.05; H, 5.36; F, 8.72; N, 13.39

#### EXAMPLE 17

To a solution of 10.51 g of *trans*- $\beta$ -dimethylamino - 5 - fluoro - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 150 ml portions of water and 150 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to give 5.23 g of a brown solid.

Distillation (b.p. 85°/0.5 mm) yielded 5.01 g of a yellowish solid which, upon crystallization from pentane, yielded 2.36 g of 5-fluoroindole as white leaflets having a melting point of 46.5—47°. The mother liquor was percolated through 10 g of alumina and the product eluted with ether. Sublimation of this material gave an additional 1.07 g of product having a melting point of 46—47°. Thus, the total yield was 3.44 g (51%).

#### EXAMPLE 18

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 11.18 g of 4-methyl-3-nitrobenzaldehyde dimethyl acetal, 11.8 g of N,N-dimethylformamide diethyl acetal and 50 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 8 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The dark red solid residue was triturated with cold methanol. The remaining solid was crystallized from 30 ml of ether/pentane to yield 7.22 g of *trans* - 4 - ( $\beta$  - dimethylaminovinyl) - 3 - nitrobenzaldehyde dimethyl acetal having a melting point of 67—68.5°. The residue, obtained after evaporation of the mother liquor, was crystallized from 5 ml of ether/pentane to give an additional 0.57 g of product having a melting point of 66.5—68.0°. Thus, the total yield was 7.79 g (55%).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_4$ :

C, 58.63; H, 6.81; N, 10.52

Found:

C, 58.69; H, 6.75; N, 10.40

#### EXAMPLE 19

To a solution containing 5.31 g of *trans* - 4 - ( $\beta$  - dimethylaminovinyl) - 3 - nitrobenzaldehyde dimethyl acetal in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and was washed several times with benzene. The residue, obtained by the evaporation of the benzene filtrate, was chromatographed on 150 g of alumina. The fractions eluted with 20% benzene/hexane followed by ether were combined and rechromatographed on 300 g of alumina. The fractions eluted with ether were combined (1.33 g) and crystallized from ether/pentane to give 0.76 g (26%) of 6-formylindole having a melting point of 127—128.5°.

#### EXAMPLE 20

To a solution containing 6.65 g of *trans* -

- 4 - ( $\beta$  - dimethylaminovinyl) - 3 - nitrobenz - aldehyde dimethyl acetal in 125 ml of benzene were added 1.0 g of potassium carbonate and 0.332 g of 10% palladium on carbon. The suspension was stirred under an atmosphere of hydrogen. After the hydrogen absorption ceased, the catalyst was removed by filtration and was washed several times with benzene. Evaporation of the filtrate gave 4.95 g of residue which, on short-path distillation, yielded 1.74 g of a purplish oil which crystallized on cooling. Crystallization of this solid from 10 ml of ether/(petroleum ether) yielded 1.18 g of a white solid having a melting point of 62—63.5°. The mother liquor was applied to 10 g of alumina and an additional 0.52 g of the same product was eluted with 1:1 ether/(petroleum ether). Recrystallization from ether/(petroleum ether) yielded 1.34 g (31%) of 6-formylindole dimethyl acetal having a melting point of 62—63.5°.
- Anal. Calcd. for  $C_{17}H_{19}NO_2$ :  
C, 69.09; H, 6.35; N, 7.33
- Found:  
C, 69.22; H, 6.76; N, 7.34

#### EXAMPLE 21

- In a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 17.9 g of 2-nitro-*p*-cymene, 17.9 g of  $N,N$ -dimethylformamide dimethyl acetal and 25 ml of  $N,N$ -dimethylformamide. The flask was immersed in an oil bath at 150° for 42 hours during which time 8 ml of methanol distilled. The contents of the flask were transferred to a CLAISEN flask. Vacuum distillation, after removal of the more volatile components up to 130°/0.06 mm, afforded 19.61 g (84%) of *trans* -  $\beta$  - dimethylamino - 4 - isopropyl-2-nitrostyrene as a red liquid (b.p. 138—140°/0.06 mm). An analytical sample obtained from a previous experiment gave:
- Anal. Calcd. for  $C_{17}H_{19}N_2O_2$ :  
C, 66.64; H, 7.74; N, 11.95
- Found:  
C, 66.69; H, 7.89; N, 11.95

#### EXAMPLE 22

- A solution containing 11.71 g of *trans*- $\beta$ -dimethylamino - 4 - isopropyl - 2 - nitrostyrene in 125 ml of benzene and 0.234 g of 10% palladium on carbon were stirred under a hydrogen atmosphere. After hydrogen absorption ceased, the catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 50 ml portions of 1N sulfuric acid, 100 ml of water and 50 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered, and evaporated to give 7.47 g of a

green semi-solid. Trituration of this material with three 20 ml portions of ether gave 6.8 g of an ether-soluble green liquid which was distilled (b.p. 79—87°/0.05 mm). Crystallization of the yellow distillate from pentane yielded 4.04 g (51%) of 6-isopropylindole having a melting point of 40—41°.

Anal. Calcd. for  $C_{17}H_{19}N$ :  
C, 82.97; H, 8.23; N, 8.80

Found:  
C, 83.20; H, 8.23; N, 8.91

#### EXAMPLE 23

In a 250 ml three-necked flask fitted with a thermometer, a 15 cm VIGREUX column connected to a descending condenser and a receiver with a nitrogen inlet were placed 25.1 g of 4 - methyl - 3 - nitro - anisole, 42.0 g of 88%  $N,N$ -dimethylformamide diethyl acetal and 150 ml of  $N,N$ -dimethylformamide. The flask was immersed in an oil bath, preheated to 165°, for 70 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation under nitrogen until the head temperature rose above 95°/0.05 mm. The remaining dark liquid was then transferred to a CLAISEN flask and distilled to yield 21.2 g (64%) of *trans*- $\beta$ -dimethylamino-4-methoxy-2-nitrostyrene as a dark red liquid having a boiling point of 152°/0.06 mm.

Anal. Calcd. for  $C_{17}H_{19}N_2O_2$ :  
C, 59.45; H, 6.35; N, 12.60

Found:  
C, 59.68; H, 6.53; N, 12.64

#### EXAMPLE 24

To a solution of 13.478 g of *trans*- $\beta$ -dimethylamino - 4 - methoxy - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until hydrogen absorption ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 100 ml portions of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 6.7 g of a yellowish solid which, on distillation, yielded 5.64 g (63%) of 6-methoxyindole as an almost white solid having a melting point of 88—90°.

#### EXAMPLE 25

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and re-



ceiver with a nitrogen inlet was charged with 16.7 g of 5-methoxy-2-nitrotoluene, 32.3 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath, preheated to 165°, for 22 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The resulting dark red solid residue was crystallized from 100 ml of ether and 75 ml of petroleum ether and yielded 17.0 g of *trans*- $\beta$ -dimethylamino - 5 - methoxy - 2 - nitrostyrene as red crystals having a melting point of 67.5—69.5°. The residue, obtained after evaporation of the mother liquor, was triturated with 10 ml of ice-cold methanol. Recrystallization of the resulting solid (2.8 g) from 10 ml of methanol gave an additional 2.7 g of product having a melting point of 68—69°. Thus, the total yield was 19.7 g (89%).

Anal. Calcd. for  $C_{11}H_{14}N_2O_3$ :

C, 59.45; H, 6.35; N, 12.60

Found:

C, 59.53; H, 6.39; N, 12.65

#### EXAMPLE 26

To a solution containing 11.11 g of *trans*- $\beta$  - dimethylamino - 5 - methoxy - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle were added 230 mg of 10% palladium on carbon. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen had ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 100 ml portions of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 5.45 g of a brown solid. Distillation yielded 5.26 g (72%) of 5-methoxyindole as a slightly yellowish liquid having a boiling point of 108°/0.3 mm which crystallized on cooling to an off-white solid having a melting point of 56—57°.

#### EXAMPLE 27

A) The preparation of the starting material:

A solution containing 75.0 g of piperonal, 200 ml of glacial acetic acid and 1 ml of concentrated hydrochloric acid was shaken with 4 g of 10% palladium on carbon in an autoclave under an initial hydrogen pressure of 35 atmospheres until hydrogen absorption ceased. The catalyst was removed by filtration.

The filtrate was transferred to a three-necked flask fitted with a thermometer, mechanical stirrer and a dropping funnel. A solu-

tion containing 80.0 ml of concentrated nitric acid in 200 ml of glacial acetic acid was added to the reaction vessel with stirring over a period of 1 hour. The reaction vessel was maintained below 10° by means of an ice-acetone bath. After the addition was complete, the reaction mixture was allowed to reach room temperature and was then poured over a mixture of sodium hydroxide and ice. The resulting suspension was extracted with four 1000 ml portions of methylene chloride. The combined organic phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give a yellow solid which, after crystallization from 300 ml of ethanol, gave 76.5 g (84%) of 4,5-methylenedioxy - 2 - nitrotoluene as yellow needles having a melting point of 85—86.5°.

B) The condensation:

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser with a receiver and a nitrogen inlet was charged with 18.1 g of 4,5-methylenedioxy-2-nitrotoluene, 20 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath at 165° for 17.5 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.05 mm. The residue was crystallized from 300 ml of ethanol to give 17.0 g (72%) of *trans*- $\beta$ -dimethylamino - 4,5 - methylenedioxy - 2 - nitrostyrene as red-brown crystals having a melting point of 114—116°.

Anal. Calcd. for  $C_{11}H_{12}N_2O_4$ :

C, 55.93; H, 5.12; N, 11.86

Found:

C, 56.09; H, 5.17; N, 11.56

#### EXAMPLE 28

A solution containing 11.83 g of *trans*- $\beta$ -dimethylamino - 4,5 - methylenedioxy - 2 - nitrostyrene in 250 ml of benzene was shaken with 1 teaspoonful of RANEY nickel under an initial hydrogen pressure of 3.5 atmospheres until hydrogen absorption ceased. The catalyst was removed by filtration and washed several times with benzene. The filtrate and washings were washed with two 100 ml portions of 1M sulfuric acid, 100 ml of water and 100 ml of 10% sodium bicarbonate. The combined organic phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 5.52 g of a brown solid. A solution of the residue in benzene was percolated through a column of alumina. The eluate, after evaporation of the solvent, was sublimed at 110°/0.2 mm to give 5.2 g of a white solid which, upon crystallization from (methylene chloride)/*hexane*, yielded 4.50 g. (50%) of 5,6-methylenedioxyindole as white needles having a melting point of 109.5—110.5°.

## EXAMPLE 29

A 250 ml three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 15.22 g of 3-nitro-*o*-xylene, 20.00 g of N,N-dimethylformamide diethyl acetal and 100 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 160°, for 24 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation until the head temperature began to rise above 90°/0.1 mm. Further distillation yielded 14.54 g (70%) of *trans*- $\beta$ -dimethylamino - 6 - methyl - 2 - nitrostyrene as a dark red liquid having a boiling point of 108°/0.05 mm.

Anal. Calcd. for  $C_{11}H_{13}N_2O_2$ :

C, 64.06; H, 6.84; N, 13.58

Found:

C, 63.79; H, 7.28; N, 13.71

## EXAMPLE 30

To a solution containing 9.327 g of *trans*- $\beta$ -dimethylamino - 6 - methyl - 2 - nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added half a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen had ceased. The catalyst was removed by filtration and washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, two 100 ml portions of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 150 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 3.89 g of a brown oil which, after two distillations, yielded 3.37 g (57%) of 4-methylindole as a yellow liquid having a boiling point of 82°/0.4 mm.

## EXAMPLE 31

A 500 ml three-necked flask fitted with a thermometer, a 15 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet was charged with 30.23 g of 2-nitro-*m*-xylene, 64.77 g of N,N-dimethylformamide diethyl acetal and 200 ml of N,N-dimethylformamide. The flask was then immersed in an oil bath, preheated to 165°, for 46 hours. The pot temperature was maintained above 140° by continuous distillation of the ethanol formed.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The resulting dark red liquid residue was distilled under a vacuum, the fore-run (15.32 g, b.p. 93—99°/0.02 mm) was a mixture of *trans*- $\beta$ -dimethylamino - 3 - methyl - 2 - nitro -

styrene and 2-nitro-*m*-xylene (ratio of 3:5 respectively). Subsequent fractions yielded 16.60 g (40%) of *trans*- $\beta$ -dimethylamino-3-methyl - 2 - nitrostyrene as a red liquid (b.p. 116—117°/0.04 mm) which crystallized on cooling and had a melting point of 75—77°.

Anal. Calcd. for  $C_{11}H_{13}N_2O_2$ :

C, 4.06; H, 6.84; N, 13.58

Found:

C, 63.95; H, 6.70; N, 13.77

## EXAMPLE 32

To a solution containing 10.31 g of *trans*- $\beta$ -dimethylamino - 3 - methyl - 2 - nitrostyrene in 250 ml of benzene were added 103 mg of 10% palladium on carbon. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen had ceased. The catalyst was removed by filtration and was washed several times with benzene. The benzene filtrate was then extracted with two 100 ml portions of 1M sulfuric acid, 100 ml of water and 100 ml of 10% sodium bicarbonate solution. The aqueous phases were back-washed with 100 ml of benzene in a countercurrent manner. The combined benzene phases were dried ( $Na_2SO_4$ ), filtered and evaporated to give 4.628 g of residue which, on distillation under a vacuum, gave 4.203 g (b.p. 109°/0.9 mm) of a light tan solid. Filtration of the distillate through 50 g of alumina and crystallization from 30 ml of ether/(petroleum ether) gave 3.15 g (48 per cent) of 7-methylindole as white crystals having a melting point of 83—84°.

## EXAMPLE 33

A 1 liter three-necked flask fitted with a thermometer and a 15 cm VIGREUX column connected to a descending condenser with a receiver and nitrogen inlet was charged with 98.6 g of 4,5-dimethoxy-2-nitrotoluene, 500 ml of N,N-dimethylformamide and 120 g of N,N-dimethylformamide dimethyl acetal. The temperature was maintained at 140° for 42 hours. The volatile compounds were removed by vacuum distillation at 25°/0.1 mm to give a solid residue of crude *trans*- $\beta$ -dimethylamino-4,5-dimethoxy-2-nitrostyrene.

From a previous experiment, an analytical sample of *trans*- $\beta$ -dimethylamino - 4,5 - dimethoxy-2-nitrostyrene, a red solid, m.p. 125—126°, was obtained by crystallization from methanol.

Anal. Calcd. for  $C_{12}H_{14}N_2O_4$ :

C, 57.13; H, 6.39; N, 11.11

Found:

C, 57.47; H, 6.65; N, 11.35

## EXAMPLE 34

To a solution of the crude *trans*- $\beta$ -dimethylamino - 4,5 - dimethoxy - 2 - nitrostyrene obtained according to Example 33 in 2.0 liters of benzene were added 10 g of

10% palladium on carbon and the suspension was shaken under an initial hydrogen pressure of 7 atmospheres. After hydrogen absorption ceased (3 equivalents), the catalyst was filtered and washed with 2 liters of benzene. The combined filtrate and washings were concentrated to 2 liters *in vacuo* and the organic phase washed with three 300 ml portions of 1N sulfuric acid, 200 ml of 1N sodium hydroxide and 200 ml of water. The aqueous phases were back-washed in a countercurrent manner with 500 ml of benzene. The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ) and filtered through 280 g of silica gel. The filtrate was evaporated and the residue triturated with ether. The residual white solid was crystallized from 700 ml of benzene to give (in two crops) 24.5 g (28%) of 5,6-dimethoxyindole as white crystals, m.p. 154—155°.

#### EXAMPLE 35

In a 1 liter three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 87.3 g of 4,5-dibenzoyloxy-2-nitrotoluene, 38.0 g of N,N-dimethylformamide dimethyl acetal and 250 ml of N,N-dimethylformamide. The solution was heated at 140° for 48 hours with continuous removal of the methanol as it formed. The volatile components were removed by vacuum distillation (bath temperature 65°/0.1 mm). Crystallization of the residue from methanol (2.5 liters) yielded (two crops) 86.8 g of a red solid, m.p. 99—100°.

An analytical sample, obtained from a previous experiment, was characterized as *trans*-4,5-dibenzoyloxy- $\beta$ -dimethylamino-2-nitrostyrene, m.p. 99.5—101°.

Anal. Calcd. for  $\text{C}_{24}\text{H}_{21}\text{N}_2\text{O}_4$ :  
C, 71.27; H, 5.98; N, 6.93

Found:

C, 71.09; H, 6.30; N, 6.83

#### EXAMPLE 36

To a solution of 10.11 g of *trans*-4,5-dibenzoyloxy- $\beta$ -dimethylamino-2-nitrostyrene in 250 ml of benzene in a 500 ml PARR bottle was added a teaspoonful of RANEY nickel. The suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased. The catalyst was removed by filtration and washed several times with benzene. The benzene filtrate was extracted with three 100 ml portions of 1N sulfuric acid, 250 ml of water, three 100 ml portions of 1N sodium hydroxide and 250 ml of water. The aqueous phases were back-washed in a countercurrent manner with 100 ml of benzene.

The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to give 7.67 g of a brown solid which was dissolved in a minimum amount of benzene and chromato-

graphed on 40 g of silica gel prepared in hexane. Eluted fractions [benzene/hexane (1:1)] were pooled according to thin layer chromatography. Evaporation of the solvents and recrystallization of the residue (5.8 g) from benzene/hexane yielded 4.34 g (54%) of 5,6-dibenzoyloxyindole as white needles, m.p. 112—113°.

#### EXAMPLE 37

A 100 ml three-necked flask fitted with a reflux condenser with a nitrogen inlet was charged with 8.25 g of 4-methyl-3-nitrobenzaldehyde, 11.1 g of N,N-dimethylformamide diethyl acetal and 50 ml of N,N-dimethylformamide. The flask was immersed in an oil bath, preheated to 145°, for 45 minutes.

The volatile components were removed by vacuum distillation at 25°/0.5 mm. The dark red residue was triturated three times with 10 ml of petroleum ether. The solid residue gave, on crystallization from methanol, 5.47 g and, on recrystallization from 100 ml of (methylene chloride)/ether, 4.61 g of *trans*-4-( $\beta$ -dimethylaminovinyl)-3-nitrobenzaldehyde as red crystals having a melting point of 134—136°. The residue obtained from the mother liquors was crystallized from 12 ml of ethyl acetate to give an additional 2.21 g of product having a melting point of 134—136°. Thus, the total yield was 6.81 g (62%).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3$ :

C, 59.99; H, 5.49; N, 12.72

Found:

C, 60.23; H, 5.22; N, 12.66

#### EXAMPLE 38

In a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 6.85 g (0.05 mol) of *o*-nitrotoluene, 7.25 g (0.05 mol) of N-formylpyrrolidine dimethyl acetal and 25 ml of N,N-dimethylformamide. The flask was immersed in an oil bath at 160° for 1 hour during which time 2.8 ml of methanol distilled. Volatile components were removed by vacuum distillation from a CLAISEN flask. A portion of the residue was distilled with partial decomposition in a short-path distillation flask (bath 150°/0.1 mm). The distillate was then vaporized twice in a molecular still (bath 110°/0.04 mm), discarding a small amount of fore-run each time. In this way, 560 mg of analytically pure *trans*-2-nitro- $\beta$ -pyrrolidinostyrene were obtained as a red liquid.

Anal. Calcd. for  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2$ :

C, 66.03; H, 6.47; N, 12.84

Found:

C, 65.89; H, 6.45; N, 12.79

#### EXAMPLE 39

To a 100 ml three-necked flask fitted with

a thermometer and 8 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet were added 13.7 g (0.10 mol) of *o*-nitrotoluene, 16.0 g (0.11 mol) of *N*-formylpyrrolidine dimethyl acetal and 50 ml of *N,N*-dimethylformamide. The solution was then heated to 130–150° for 1.5 hours, maintaining the temperature by continuous distillation of the methanol which formed during the condensation.

Removal of the volatile components by vacuum distillation (bath 50°/1 mm) gave crude *trans*-2-nitro- $\beta$ -pyrrolidinostyrene as a red liquid.

The product was dissolved in 100 ml of benzene and the solution shaken in a hydrogen atmosphere with 440 mg of 10% palladium on charcoal at an initial pressure of 3.5 atmospheres until hydrogen absorption ceased (3 equivalents). The catalyst was removed by filtration through a bed of diatomaceous silica and was washed with three 50 ml portions of benzene. The filtrate was then extracted, consecutively with two 200 ml portions of 1M sulfuric acid, two 200 ml portions of water and 100 ml of 1M sodium carbonate. The aqueous phases were back-washed in a countercurrent manner with two 200 ml portions of benzene. The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated (rotary evaporator) to give 11.0 g of a greenish solid which, on distillation, afforded 9.61 g (82%) of indole, b.p. 78°/0.3 mm, m.p. 50–51.5°.

#### EXAMPLE 40

In a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 6.85 g of *o*-nitrotoluene, 8.76 g of *N*-formylpiperidine dimethyl acetal and 25 ml of *N,N*-dimethylformamide. The flask was immersed in an oil bath at 150° for 7 hours during which time 4 ml of methanol distilled. Vacuum distillation from a CLAISEN flask afforded, after removal of the volatile components, three fractions: 2.86 g (b.p. 114–145°/0.06 mm), 0.73 g (b.p. 145–146°/0.06 mm) and 5.35 g (b.p. 146–147°/0.07 mm). The last fraction was analytically pure *trans*-2-nitro- $\beta$ -piperidinostyrene.

Anal. Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$ :  
C, 67.22; H, 6.94; N, 12.06

Found:

C, 67.03; H, 7.08; N, 12.06

#### EXAMPLE 41

In a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX distillation head connected to a descending condenser and receiver with a nitrogen inlet were placed 13.40 g (0.10 mol) of *o*-nitrotoluene, 13.40 g (0.10 mol) of *N*-formylpiperidine dimethyl acetal and 25 ml of *N,N*-dimethyl-

formamide. The solution was then heated to 130–150° for 3 hours allowing the methanol to distil as it formed. Removal of the volatile components by vacuum distillation (water bath at 60°/0.5 mm) afforded crude *trans*-2-nitro- $\beta$ -piperidinostyrene as a red liquid.

The crude *trans*-2-nitro- $\beta$ -piperidinostyrene was dissolved in 250 ml of benzene, 0.460 g of 5% palladium on charcoal were added and the suspension was shaken under an initial hydrogen pressure of 3.5 atmospheres until the absorption of hydrogen ceased (3 equivalents). The catalyst was removed by filtration and was washed several times with benzene. The filtrate was extracted with three 100 ml portions of 1M sulfuric acid, 100 ml of water, two 100 ml portions of 1N sodium hydroxide and 100 ml of water. The aqueous phases were back-washed in a countercurrent manner with 100 ml of benzene. The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to give 9.06 g of a brown solid. Distillation in a CLAISEN flask gave 7.66 g (70%) of indole, b.p. 60–65°/0.06 mm, b.p. 44–49°.

#### EXAMPLE 42

To a 100 ml three-necked flask fitted with a thermometer and 8 cm VIGREUX column connected to a descending condenser and receiver with a nitrogen inlet were added 8.35 g (50 mmol) of 3-methyl-4-nitroanisole, 8.0 g (55 mmol) of *N*-formylpyrrolidine dimethyl acetal and 25 ml of *N,N*-dimethylformamide. The solution was heated at 135° for two hours with continuous distillation of the methanol which formed during the condensation.

Removal of the volatile components under a vacuum (40° bath/1 mm) and recrystallization of the red residue from 75 ml of methanol gave, in two crops, 11.7 g (94%) of red needles, m.p. 71–72°.

Recrystallization of a portion of the first crop from methanol afforded an analytical sample of *trans*-5-methoxy-2-nitro- $\beta$ -pyrrolidinostyrene, m.p. 71–72°.

Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$ :

C, 2.87; H, 6.58; N, 11.24

Found:

C, 2.87; H, 6.58; N, 11.24

#### EXAMPLE 43

A solution of 8.35 g (0.050 mol) of 3-methyl-4-nitro-anisole, 14.58 g (0.062 mol) of *N,N*-dimethylformamide dioneopentyl acetal and 50 ml of *N,N*-dimethylformamide was heated at reflux under a nitrogen atmosphere for 41 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components 4.75 g of a red liquid (b.p. 152°/0.04 mm) which crystallized on scratching to give a solid, m.p. 61–65°. Recrystallization from 70 ml of ether/(petroleum ether) gave 3.70 g (33%)

of *trans* -  $\beta$  - dimethylamino - 5 - methoxy - 2-nitrostyrene, m.p. 68.5—69.5°.

#### EXAMPLE 44

A solution of 3.0 g (0.018 mol) of 3-methyl-4-nitro-anisole, 5.1 g (0.020 mol) of N,N-dimethylformamide dicyclohexyl acetal and 25 ml of N,N-dimethylformamide was heated at reflux under a nitrogen atmosphere for 40 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 1.89 g of a red liquid (b.p. 158°/0.04 mm) which crystallized on scratching to give a solid, m.p. 61—64°. Recrystallization from 10 ml of ether and 7 ml of petroleum ether gave 1.46 g (36%) of *trans* -  $\beta$  - dimethylamino - 5-methoxy-2-nitrostyrene, m.p. 67.5—69°.

#### EXAMPLE 45

A solution of 16.71 g (0.10 mol) of 3-methyl-4-nitro-anisole, 30.00 g (0.11 mol) of N,N-dimethylformamide dibenzyl acetal and 50 ml of N,N-dimethylformamide was heated at reflux under a nitrogen atmosphere for 17 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 9.42 g of a red liquid (b.p. 158°/0.10 mm) which gave a tacky solid upon scratching. Recrystallization from 150 ml of ether/(petroleum ether) gave, in two crops, 7.15 g (32%) of *trans*- $\beta$ -dimethylamino - 5 - methoxy - 2 - nitrostyrene, m.p. 68.0—69.5°.

#### EXAMPLE 46

A solution of 8.35 g (50 mmol) of 3-methyl-4-nitro-anisole, 8.76 g (75 mmol) of N,N-dimethylformamide ethylene acetal (2-dimethylamino-1,3-dioxolane) and 25 ml of N,N-dimethylformamide was heated at 150° under a nitrogen atmosphere for 53 hours and was then transferred to a CLAISEN flask. Vacuum distillation afforded, after removal of the volatile components, 4.00 g of a red liquid (b.p. 149°/0.07 mm) which formed a gummy solid on scratching. Crystallization from 15 ml of methanol gave 1.57 g (14%) of *trans*- $\beta$ -dimethylamino - 5 - methoxy - 2 - nitro - styrene, m.p. 68—69°.

#### EXAMPLE 47

In a 500 ml three-necked flask fitted with a thermometer and mechanical stirrer were placed 19.2 g (0.10 mol) of *trans*- $\beta$ -dimethylamino-2-nitrostyrene, 100 ml of ethanol and 100 ml of glacial acetic acid followed by 41.9 g (0.75 mol) of purified iron powder over a period of 5 minutes. The suspension was stirred for 2 hours during which time the temperature rose to 45° (the temperature was controlled by a water bath). Then 30 ml of 1N hydrochloric acid were added. The red colour discharged and the temperature rose to about 45°. The mixture was allowed to

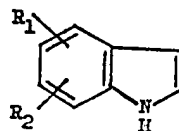
stand for 18 hours and was then poured on to 1 liter of ice-water. To the resulting slurry were added 250 ml of benzene and then both phases were filtered through a bed of diatomaceous silica. The benzene layer was separated and the aqueous layer extracted once more with 200 ml of benzene. The combined benzene extracts were washed successively with two 200 ml portions of 0.5N sulfuric acid and 100 ml of 10% potassium carbonate. The aqueous phases were back-washed in a countercurrent manner with 100 ml of benzene. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to give 4.2 g of a brown solid which was dissolved in a minimum amount of benzene and chromatographed on 50 g of alumina. Eluted fractions containing indole [(petroleum ether)/benzene, (9:1)] were pooled according to the thin layer chromatography. Evaporation of the solvents and sublimation of the residue (40—50° oil bath/0.03 mm) yielded 2.02 g (17%) of indole as white plates, m.p. 51.5—52.5°.

#### EXAMPLE 48

To a stirred solution of 19.2 g (0.10 mol) of *trans* -  $\beta$  - dimethylamino - 2 - nitro - styrene in 500 ml of water and 200 ml of methanol was added portionwise over 5 minutes a mixture of 55.0 g (0.315 mol) of sodium dithionite and 28.0 g (0.20 mol) of potassium carbonate while maintaining the temperature at 60—65° by means of a water bath. Since a suspension formed, 300 ml of methanol were added and stirring was continued for 0.75 hour. To the mixture were added 20 ml of 30% ammonium hydroxide and, after removal of the methanol with a rotary evaporator, an additional 60 ml of 30% ammonium hydroxide. The solution was then extracted with three 400 ml portions of benzene. The organic phases were back-washed in a countercurrent manner with 100 ml of water. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to give 3.5 g of a dark brown solid which was dissolved in a minimum amount of benzene and chromatographed on 60 g of alumina. Eluted fractions (petroleum ether) containing indole were pooled according to thin layer chromatography. Evaporation of the solvents and sublimation of the residue (2.4 g) yielded 2.14 g (18%) of indole, m.p. 50—52°.

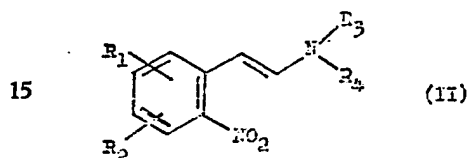
#### WHAT WE CLAIM IS:—

1) A process for the manufacture of indoles of the general formula



(I)

wherein  $R_1$  and  $R_2$  independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkylamino, lower alkoxy, carbonylamino, aryl-lower alkoxy, carbonylamino, acylamino, N-lower alkyl, acylamino, di-lower alkylformamidino or di-lower alkoxy, methyl or  $R_1$  and  $R_2$  together represent lower alkylenedioxy, which process comprises treating an *ortho*-nitro- $\beta$ -amino-styrene of the general formula



wherein  $R_1$  and  $R_2$  have the significance given earlier in this claim and  $R_3$  and  $R_4$  independently represent lower alkyl or  $R_3$  and  $R_4$  together represent lower alkylene, with a reducing agent.

2) A process as claimed in claim 1, wherein the *ortho* - nitro -  $\beta$  - aminostyrene of formula II is hydrogenated in the presence of a suitable hydrogenation catalyst.

3) A process as claimed in claim 2, wherein the hydrogenation catalyst consists of chromium, molybdenum, tungsten, platinum, palladium, rhodium, cobalt, nickel or ruthenium, their oxides or combinations thereof.

4) A process as claimed in claim 3, wherein palladium or RANEY nickel is used as the hydrogenation catalyst.

5) A process as claimed in any one of claims 2 to 4 inclusive, wherein the hydrogenation catalyst is supported on carbon.

6) A process as claimed in any one of claims 2 to 5 inclusive, wherein the hydrogenation is carried out in the presence of an inert solvent.

7) A process as claimed in claim 6, wherein the solvent is an alkanol, a hydrocarbon, ethyl acetate or N,N-dimethylformamide.

8) A process as claimed in claim 7, wherein the solvent is benzene.

9) A process as claimed in claim 1, wherein the *ortho*-nitro- $\beta$ -aminostyrene of formula II is reduced with iron, zinc or tin in an organic or inorganic acid, with stannous chloride in hydrochloric acid, with sodium dithionite or with sodium or ammonium sulfide or hydro-sulfide.

10) A process as claimed in claim 9, wherein the reduction is carried out in the presence of water or a water miscible solvent.

11) A process as claimed in claim 10, wherein the water miscible solvent is an alkanol or tetrahydrofuran.

12) A process as claimed in any one of claims 1 to 11 inclusive, wherein  $R_3$  and  $R_4$  each represent lower alkyl.

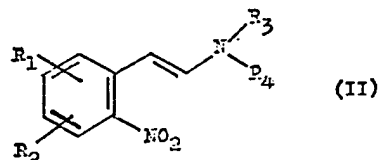
13) A process as claimed in claim 12, wherein  $R_3$  and  $R_4$  each represent methyl.

14) A process as claimed in any one of claims 1 to 13 inclusive, wherein  $R_1$  and  $R_2$  independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy, carbonyl, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkyl, amino, lower alkoxy, carbonylamino, aryl-lower alkoxy, carbonylamino, acylamino, N-lower alkyl, acylamino, di-lower alkylformamidino or dimethoxymethyl or  $R_1$  and  $R_2$  together represent lower alkylenedioxy.

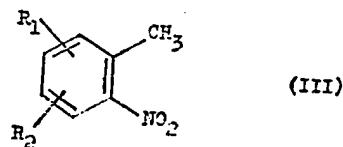
15) A process as claimed in claim 14, wherein  $R_1$  and  $R_2$  independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, acyloxy, formyl, aroyl, halogen, amino or acylamino or  $R_1$  and  $R_2$  together represent lower alkylenedioxy.

16) A process as claimed in claim 15, wherein  $R_1$  and  $R_2$  each represent hydrogen.

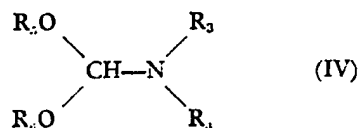
17) A process for the preparation of *ortho*-nitro- $\beta$ -amino-styrenes of the general formula



wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  have the significance given in claim 1, which process comprises condensing an *ortho*-nitrotoluene of the general formula



wherein  $R_1$  and  $R_2$  have the significance given in claim 1, with a formamide acetal of the general formula



wherein  $R_5$  and  $R_6$  have the significance given in claim 1 and  $R_3$  and  $R_4$  independently represent lower alkyl, aralkyl or cycloalkyl or  $R_3$  and  $R_4$  together represent lower alkylene.

18) A process as claimed in claim 17,

wherein the condensation is effected in the presence of a polar aprotic solvent.

19) A process as claimed in claim 18, wherein the solvent is N,N-dimethylformamide, diethyleneglycol dimethyl ether or hexamethylphosphortriamide.

20) A process as claimed in any one of claims 17 to 19 inclusive, wherein the condensation is conducted at a temperature in the range of from 100°C to 160°C.

21) A process as claimed in any one of claims 17 to 20 inclusive, wherein at least one of R<sub>3</sub> and R<sub>4</sub> represents other than methyl when one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen and the other represents hydrogen or methyl in the 3-position.

22) A process as claimed in claim 21, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy-carbonyl, carbamoyl, halogen, amino, mono-lower alkyl-amino, di-lower alkyl-amino, lower alkoxy carbonylamino, aryl-lower alkoxy-carbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino or dimethoxymethyl or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy and R<sub>3</sub> and R<sub>4</sub> independently represent lower alkyl or R<sub>5</sub> and R<sub>6</sub> together represent lower alkylene.

23) A process as claimed in claim 21 or claim 22, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, hydroxy lower alkoxy, aryl-lower alkoxy, acyloxy, formyl, aroyl, halogen, amino or acylamino or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy.

24) A process as claimed in any one of claims 21 to 23 inclusive, wherein R<sub>1</sub> and R<sub>2</sub> each represent hydrogen.

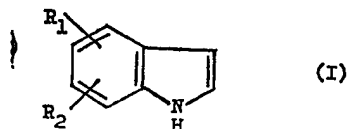
25) A process as claimed in any one of claims 21 to 24 inclusive, wherein R<sub>3</sub> and R<sub>4</sub> each represent lower alkyl.

26) A process as claimed in any one of claims 21 to 23 inclusive and claim 25, wherein R<sub>3</sub> and R<sub>4</sub> each represent methyl.

27) A process as claimed in any one of claims 17 to 20 inclusive, wherein R<sub>3</sub> and R<sub>4</sub> each represent methyl and one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen and the other represents hydrogen or methyl in the 3-position.

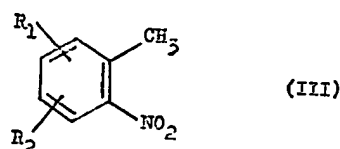
28) A process as claimed in claim 27, wherein R<sub>5</sub> and R<sub>6</sub> independently represent lower alkyl or R<sub>5</sub> and R<sub>6</sub> together represent lower alkylene.

29) A process for the manufacture of indoles of the general formula



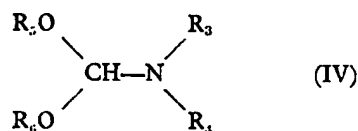
wherein R<sub>1</sub> and R<sub>2</sub> have the significance given in claim 1,

which process comprises condensing an *ortho*-nitrotoluene of the general formula

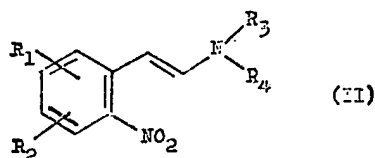


wherein R<sub>1</sub> and R<sub>2</sub> have the significance given in claim 1,

with a formamide acetal of the general formula



wherein R<sub>3</sub> and R<sub>4</sub> have the significance given in claim 1 and R<sub>5</sub> and R<sub>6</sub> have the significance given in claim 17, and treating the resulting *ortho*-nitro- $\beta$ -aminostyrene of the general formula



wherein R<sub>1</sub>, R<sub>3</sub>, R<sub>5</sub> and R<sub>6</sub> have the significance given in claim 1,

with a reducing agent.

30) A process as claimed in claim 29, wherein the condensation is effected in the presence of a polar aprotic solvent.

31) A process as claimed in claim 30, wherein the solvent is N,N-dimethylformamide, diethyleneglycol dimethyl ether or hexamethylphosphortriamide.

32) A process as claimed in any one of claims 29 to 31 inclusive, wherein the condensation is conducted at a temperature in the range of from 100°C to 160°C.

33) A process as claimed in any one of claims 29 to 32 inclusive, wherein the *ortho*-nitro- $\beta$ -aminostyrene of formula II is hydrogenated in the presence of a suitable hydrogenation catalyst.

34) A process as claimed in claim 33, wherein the hydrogenation catalyst consists of chromium, molybdenum, tungsten, platinum, palladium, rhodium, cobalt, nickel or ruthenium, their oxides or combinations thereof.

35) A process as claimed in claim 34, wherein palladium or RANEY nickel is used as the hydrogenation catalyst.

36) A process as claimed in any one of claims 33 to 35 inclusive, wherein the hydrogenation catalyst is supported on carbon.

37) A process as claimed in any one of claims 33 to 36 inclusive, wherein the hydrogenation is carried out in the presence of an inert solvent.

38) A process as claimed in claim 37, wherein the solvent is an alkanol, a hydrocarbon, ethyl acetate or N,N-dimethylformamide.

39) A process as claimed in claim 38, wherein the solvent is benzene.

40) A process as claimed in claim 29, wherein the *ortho*-nitro- $\beta$ -aminostyrene of formula II is reduced with iron, zinc or tin in an organic or inorganic acid, with stannous chloride in hydrochloric acid, with sodium dithionite or with sodium or ammonium sulfide or hydrosulfide.

41) A process as claimed in claim 40, wherein the reduction is carried out in the presence of water or a water miscible solvent.

42) A process as claimed in claim 41, wherein the water miscible solvent is an alkanol or tetrahydrofuran.

43) A process as claimed in any one of claims 29 to 43 inclusive, wherein R<sub>3</sub> and R<sub>4</sub> each represent lower alkyl.

44) A process as claimed in claim 43, wherein R<sub>3</sub> and R<sub>4</sub> each represent methyl.

45) A process as claimed in any one of claims 29 to 44 inclusive, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy carbonyl, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkylamino, lower alkoxy carbonylamino, aryl-lower alkoxy carbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino or dimethoxymethyl or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy and R<sub>3</sub> and R<sub>4</sub> independently represent lower alkyl or R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene.

46) A process as claimed in any one of claims 29 to 44 inclusive, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, formyl, aroyl, halogen, amino, or acylamino or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy.

47) A process as claimed in claim 46, wherein R<sub>1</sub> and R<sub>2</sub> each represent hydrogen.

48) A process as claimed in claim 47, wherein *o*-nitrotoluene is condensed with N,N-dimethylformamide dimethyl acetal to yield  $\beta$ -dimethylamino-2-nitrostyrene which is reduced to yield indole.

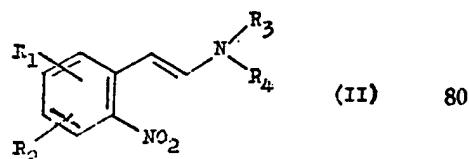
49) A process for the manufacture of the indoles of formula I in claim 1, substantially as hereinbefore described with reference to the foregoing Examples.

50) Indoles of formula I in claim 1, when manufactured by the process claimed in any one of claims 1 to 16 inclusive or any one of claims 29 to 49 inclusive.

51) A process for the preparation of the *ortho*-nitro- $\beta$ -aminostyrenes of formula II in claim 1, substantially as described with reference to the Examples.

52) *Ortho*-nitro- $\beta$ -aminostyrenes of formula II in claim 1, when prepared by the process claimed in any one of claims 17 to 28 inclusive or claim 51.

53) An *ortho*-nitro- $\beta$ -aminostyrene of the general formula



wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy carbonyl, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkylamino, lower alkoxy carbonylamino, aryl-lower alkoxy carbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino or di-lower alkoxy methyl or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy and R<sub>3</sub> and R<sub>4</sub> independently represent lower alkyl or R<sub>3</sub> and R<sub>4</sub> together represent lower alkylene, with the proviso that at least one of R<sub>3</sub> and R<sub>4</sub> is other than methyl when one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen and the other represents hydrogen or methyl in the 3-position.

54) An *ortho*-nitro- $\beta$ -aminostyrene as claimed in claim 53, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, aryl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, hydroxymethyl, aryl-hydroxymethyl, carboxy, lower alkoxy carbonyl, carbamoyl, halogen, amino, mono-lower alkylamino, di-lower alkylamino, lower alkoxy carbonylamino, aryl-lower alkoxy carbonylamino, acylamino, N-lower alkylacylamino, di-lower alkylformamidino or dimethoxymethyl or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy.

55) An *ortho*-nitro- $\beta$ -aminostyrene as claimed in claim 53 or claim 54, wherein R<sub>1</sub> and R<sub>2</sub> independently represent hydrogen, lower alkyl, hydroxy, lower alkoxy, aryl-lower alkoxy, aryloxy, acyloxy, formyl, aroyl, halogen, amino or acylamino or R<sub>1</sub> and R<sub>2</sub> together represent lower alkylenedioxy.

56) An *ortho*-nitro- $\beta$ -aminostyrene as claimed in any one of claims 53 to 55 in-



clusive, wherein  $R_1$  and  $R_2$  each represent hydrogen.

- 5 57) An *ortho*-nitro- $\beta$ -aminostyrene as claimed in any one of claims 53 to 56 inclusive, wherein  $R_3$  and  $R_4$  each represent lower alkyl.

58) An *ortho*-nitro- $\beta$ -aminostyrene as claimed in any one of claims 53 to 55 in-

clusive and claim 57, wherein  $R_3$  and  $R_4$  each represent methyl.

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